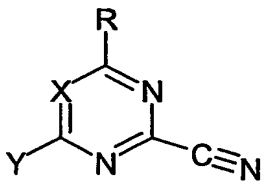
CLAIMS

1. compound of formula I, or a pharmaceutically acceptable salt or ester thereof



I

In which

R is H, -R2, -OR2 or NR1R2,

wherein R1 is H, lower alkyl or C_3 to C_{10} cycloalkyl, and

R2 is lower alkyl or C_3 to C_{10} cycloalkyl, and

wherein R1 and R2 are independently, optionally substituted by halo, hydroxy, lower alkoxy, CN, NO_2, or optionally mono- or di-lower alkyl substituted amino;

X is =N- or =C(Z)-,

wherein Z is H, -R4, -C≡C-CH_2-R5, C(P)=C(Q)-R3,

wherein

P and Q independently are H, lower alkyl or aryl,

R3 is aryl, aryl–lower alkyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl,

wherein R3 is independently, optionally substituted by one or more groups, e.g. 1-3 groups, selected from halo, hydroxy, oxo, lower alkoxy, CN or NO_2, or optionally substituted (optionally mono- or di-lower alkyl substituted amino, aryl, aryl-lower alkyl, N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein the optional substitution comprises from 1 to 3 substituents selected from halo, hydroxy, lower alkoxy, CN, NO_2, or optionally mono- or di-lower alkyl substituted amino)),

R4 is H, aryl, aryl–lower alkyl, aryl-lower-alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl, and wherein

R5 is aryl, aryl-lower alkyl, aryloxy, aroyl or N-heterocyclyl as defined above, and wherein R5 is optionally substituted by R7 which represents from 1 to 5 substitutents selected from halo, hydroxy, CN, NO_2 or oxo, or optionally substituted (lower-alkoxy,

lower-alkyl, aryl, aryloxy, aroyl, lower-alkylsulphonyl, arylsulphonyl, optionally mono- or di-lower alkyl substituted amino, or N-heterocyclyl, or N-heterocyclyl-lower alkyl, wherein N-heterocyclyl denotes a saturated, partially unsaturated or aromatic nitrogen containing heterocyclic moiety attached via a nitrogen atom thereof having from 3 to 8 ring atoms optionally containing a further 1, 2 or 3 heteroatoms selected from N, NR6, O, S, S(O) or $S(O)_2$ wherein R6 is H or optionally substituted (lower alkyl, carboxy, acyl (including both lower alkyl acyl, e.g. formyl, acetyl or propionyl, or aryl acyl, e.g. benzoyl), amido, aryl, S(O) or $S(O)_2$), and wherein the N-heterocyclyl is optionally fused in a bicyclic structure, e.g. with a benzene or pyridine ring, and wherein the N-heterocyclyl is optionally linked in a spiro structure with a 3 to 8 membered cycloalkyl or heterocyclic ring wherein the heterocyclic ring has from 3 to 10 ring members and contains from 1 to 3 heteroatoms selected from N, NR6, O, S, S(O) or $S(O)_2$ wherein R6 is as defined above), and

wherein heterocyclyl denotes a ring having from 3 to 10 ring members and containing from 1 to 3 heteroatoms selected from N, NR6, O, S, S(O) or $S(O)_2$ wherein R6 is as defined above), and

and

wherein R7 is optionally substituted by from 1 to 3 substitutents selected from halo, hydroxy, optionally mono- or di- lower-alkyl substituted amino, lower-alkyl carbonyl, lower-alkoxy or lower-alkylamido;

Y is –NR8R9,

wherein

R8 is H, or optionally substituted (lower alkyl, aryl, aryl–lower alkyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl),

wherein R8 is optionally substituted by R10 which represents from 1 to 4 substitutents selected from halo, hydroxy, CN, NO_2, -O-C(O)-, optionally substituted (lower-alkyl, C_3-C_{10}cycloalkyl, lower-alkoxy, lower-alkenyl, lower-alkynyl, optionally mono- or di-lower alkyl-substituted amino or N-heterocyclyl (as defined above),

wherein R10 is optionally substituted by R11 which represents from 1 to 4 substituents selected from halo, hydroxy, CN, NO_2, oxo, optionally substituted (optionally mono- or

di-lower alkyl-substituted amino, lower alkyl, optionally-lower alkyl substituted COOH, sulphinyl, sulphonyl, or N-heterocyclyl (as defined above))

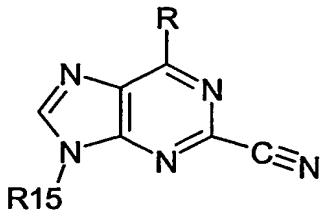
wherein R11 is optionally substituted by R12 which represents from 1 to 4 substituents selected from halo, hydroxy, CN, NO_2, oxo, hydroxy lower alkyl, C_3-C_{10}cycloalkyl, optionally lower alkyl-substituted carboxy, hydroximine, or N-heterocyclyl as defined above, and

wherein

R9 is independently H, or optionally substituted (lower alkyl, aryl, aryl–lower alkyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl), and

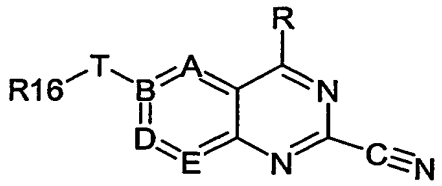
wherein R9 is optionally substituted by halo, hydroxy, oxo, lower alkoxy, CN, NO_2, or optionally mono- or di-lower alkyl substituted amino;

or Z and Y together with the carbon atoms to which they are attached are joined to provide a compound of formula I selected from,



Ib

or



Ic

wherein

R is as defined above;

R15 is lower-alkyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkyl-lower alkyl, NR20R21–lower alkyl-, where

T is –O- or a direct bond;

R16 is NR20R21–lower alkyl- or R4, both as defined above,

R20 is H, optionally substituted (lower alkyl, aryl, C_3-C_{10}cycloalkyl, lower alkoxy lower alkyl C_3-C_{10}cycloalkyl-lower alkyl or aryl lower alkyl),

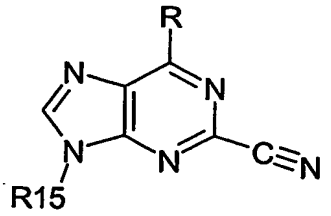
R21 is optionally substituted (lower alkyl, aryl, C_3-C_{10}cycloalkyl, lower alkoxy lower alkyl, C_3-C_{10}cycloalkyl-lower alkyl or aryl-lower alkyl), or

R20 and R21 form an N-heterocyclyl ring as hereinbefore defined,

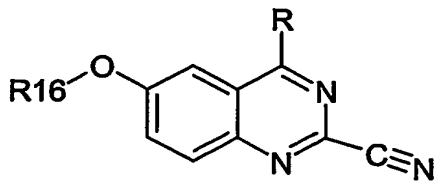
and wherein R20 or R21 are independently optionally substituted by R23 which which represents from 1 to 3 substitutents selected from halo, hydroxy, CN, NO_2, oxo, optionally mono- or di-lower alkyl substituted amino, or optionally substituted (lower-alkoxy, lower-alkyl, lower alkoxy carbonyl, aryl, aryl-lower alkyl, aryl-lower alkenyl, aryloxy, aroyl, alkylsulphonyl, arylsulphonyl or N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein N-heterocyclyl is as defined above));

A is –CH= or –C(O)-, B is –C= or –N-, D is -CH= or –C(O)- and E is –CH= or –N(R1) (where R1 is as defined above).

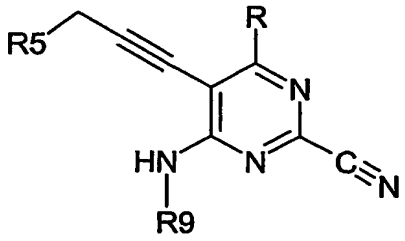
2. A compound according to claim 1 of formula Ib, Ic, II, or IV or a pharmaceutically acceptable salt or ester thereof



Ib

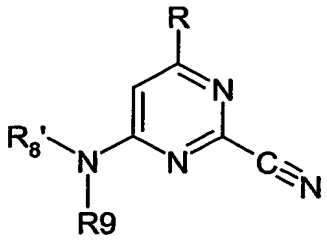


Ic



II

or



IV

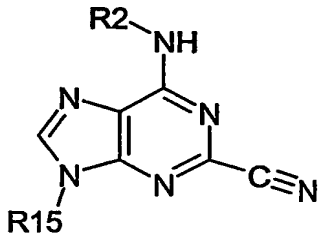
wherein

R8' is H or optionally substituted aryl-lower alkyl

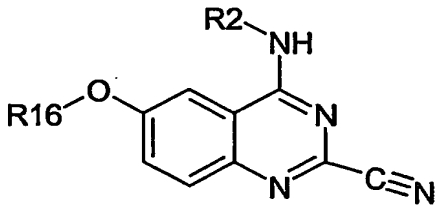
wherein R8' is optionally substituted as defined above for R8, and

the other symbols are as defined above.

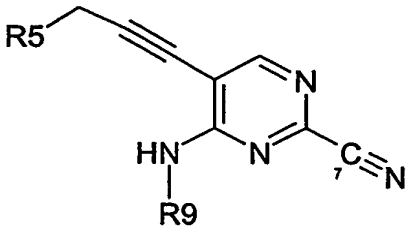
3. A compound according to claim 1 or a pharmaceutically acceptable salt or ester thereof selected from a compound of formula VI, VII, VIII or IX



VI

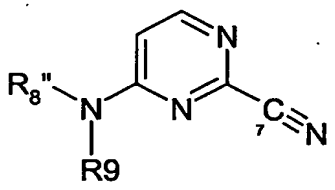


VII



VIII

or



IX

wherein the symbols are as defined above.

4. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, selected from any one of the Examples 1, 11,12, 13, .

5. A compound according to claim 1 for use as a pharmaceutical.

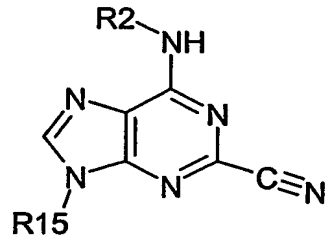
6. A pharmaceutical composition comprising a compound according to claim 1 as an active ingredient.

7. A method of treating a patient suffering from or susceptible to a disease or medical condition in which cathepsin K is implicated, comprising administering an effective amount of a compound according to claim 1 to the patient.

8. The use of a compound according to claim 1 for the preparation of a medicament for therapeutic or prophylactic treatment of a disease or medical condition in which cathepsin K is implicated.

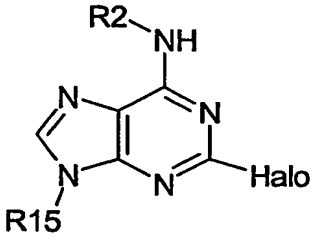
9. A process for the preparation of a compound of formula I or a salt or ester thereof which comprises

i) for the preparation of compounds of formula VI or pharmaceutically acceptable salts or esters thereof



VI

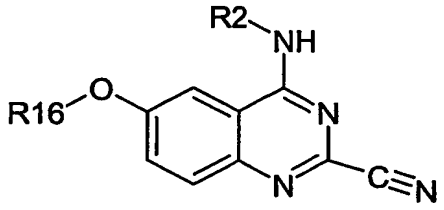
wherein R2 and R15 are as defined above, cyanation of a corresponding 2-halo precursor of formula XIV



XIV

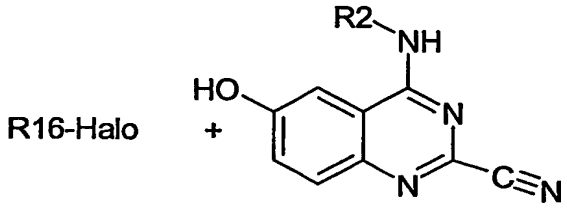
wherein R2 and R15 are as defined above and Halo is preferably Cl;

ii) for preparation of compounds of formula VII or pharmaceutically acceptable salts or esters thereof



VII

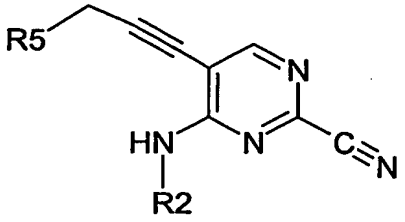
wherein R2 and R16 are as defined above, coupling of a 6-hydroxy precursor of formula XV with an R16-Halo precursor



XV

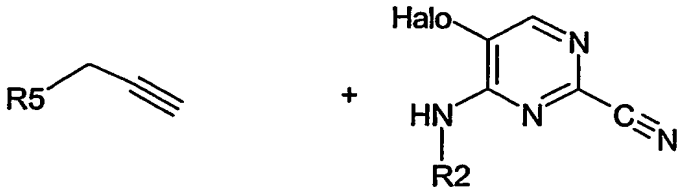
wherein R2 and R16 are as defined above and Halo is preferably Cl;

iii) for the preparation of compounds of formula VIII or pharmaceutically acceptable salts or esters thereof



VIII

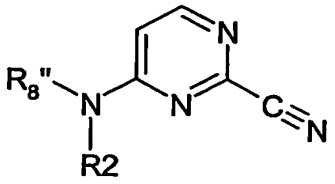
wherein R2 and R5 are as defined above, coupling of a 5-halopyrimidine precursor of formula XVI with a corresponding R5-CH_2-C≡CH propyne



XVI

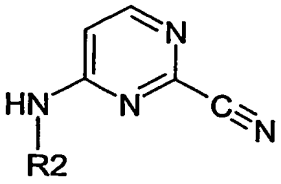
wherein R2 and R5 are as defined above and Halo is preferably Br;

iv) for the preparation of compounds of formula IX or pharmaceutically acceptable salts or esters thereof



IX

wherein R2 is as defined above and R8" is optionally substituted aryl-lower alkyl as defined above for R8', coupling of a secondary amine precursor of formula XVII



XVII

wherein R2 is as defined above, with a corresponding R8"-Halo precursor, wherein Halo is preferably I;

v) thereafter, if desired, converting the product obtained into a further compound of formula I, or into a salt or ester thereof.

All novel products, processes and uses substantially as herein described with particular reference to the Examples.